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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/216,609	12/21/1998	HANS JOHN HANSEN	018733/0734	9388

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EXAMINER
YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
1642	24

DATE MAILED: 06/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/216,609	HANSEN, HANS JOHN	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-26,29 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-26,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed 10/15/2002 (paper no. 23) is acknowledged and entered into the record. Upon further review and reconsideration, the finality of the instant application is withdrawn in view of new rejections being cited in this instant office action.

2. Claims 1-22, 27, 28, and 31-53 are canceled without prejudice or disclaimer and claims 23-26 and 29-30 are pending and examined on the merits.

Claim Rejections Withdrawn - 35 USC § 103

3. The rejection of claims 1-2, 5, 7, 14, 45-46, and 49-52 under 35 USC 103 (a) as being obvious over Iwasa *et al* in view of Bosslet *et al* or Blakey *et al* and further in view of Potter *et al* is withdrawn in view of the cancellation to the claims.

Claim Rejections Maintained – Double Patenting

4. The rejection of claims 1-6, 11, 12, 16-18, 20, 31-34, 36, 39, 42-44, 46, 49 and 53 under the judicially created doctrine of obviousness type double patenting is withdrawn, but is newly applied to claims 23-26, and 29-30. The claims are drawn to a method of targeting a multispecific targeting to a specific cancer associated target protein comprising at least two first binding sites and at least one second binding site for an enzyme. The claims are also drawn to a method wherein there is/are two different multispecific targeting proteins that bind to different targets, at least two different second binding sites that bind to different enzymes, and at least two different multispecific targeting protein with a first binding site binding to two different targets and at least

second binding site binding to a specific enzyme. Claims 1-26 of US Patent 5,851,527 represents a species of multispecific targeting proteins of which fall within the scope of the generic multispecific proteins claimed in the instant invention.

NEW ARGUMENTS

Claim Rejections - 35 USC § 102

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 23-26 arerejected under 35 U.S.C. 102(b) as being anticipated by Bagshawe KD *et al* (WO 89/10140). Claims are drawn to a method comprising the steps of administering at least one multispecific targeting protein comprising at least two first binding sites and at least one second binding site that which binds to at least one enzyme; optionally administering a clearing agent; administering an enzyme; optionally administering a clearing agent, and administering a prodrug wherein the enzyme administered would act on the said prodrug. The claims are also drawn to a method wherein there are at least two multispecific targeting proteins each of which binds to at least one enzyme, wherein there is at least one multispecific targeting protein with at least one first binding site and at least two second binding sites that bind to two different enzymes, and wherein there are at least two multispecific targeting protein with at least one first binding site of which binds to at least two different enzymes.

Bagshawe *et al* disclose a three component system for the administration and treatment of cancer using an antibody directed enzyme prodrug therapy. The components are: a first component comprising one or more molecular configuarations

that are complementary to molecular configurations associated with malignant cells and one or more catalytic sites; a second component that inactivates or helps the clearance of the first component; and a third component which is a substrate for the catalytic sites of the first component. Bagshawe *et al* further disclose that the first component can be bispecific, wherein there is specificity for a tumor marker on a malignant cell and specificity for an enzyme, in what Bagshawe *et al* calls "indirect linkage" (see page 5). Bagshawe *et al* also disclose that the first component can be bivalent compounds, wherein there is dual specificity one for tumor marker and one for an enzyme (see page 5). Bagshawe *et al* also specifically discusses the use of clearing agents (see page 11) wherein said agents aid in the removal of complexes from the plasma. And finally, Bagshawe *et al* discloses that more than one type of each component can be include in the administration.

Claim Rejections - 35 USC § 103

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Claims 23-26 and 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bagshawe *et al* in view of Tsuji *et al* (J. Pharmacobiodyn 1991 Jun;14(6):341-9) and Houba *et al* (Bioconjugate Chem 1996;7:606-611). See above for limitations to claims 23-26. The claims also further limit the enzymes to esterase and glucuronidase and the prodrug to CPT-11. See above for Bagshawe *et al*

disclosure. Bagshawe *et al* however do not teach the use of esterase, glucuronidase or of the prodrug CPT-11.

Tsuji *et al* teaches the discovery of a CPT-11 converting enzyme and that this enzyme is an esterase. Houba *et al* teaches the use of glucuronidase-antibody conjugates in antibody enzyme/prodrug therapy.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art would have found it obvious to combine the different reference because a method of administering a multispecific targeting protein and an enzyme that converts an inactive drug to an active one at the site of a tumor was well known and practiced under a procedure known as ADEPT in addition to the teachings of Bagshawe *et al*. Because Bagshawe *et al* taught the general premises of the procedure, the only missing components were the enzyme types and the prodrug. Both Tsuji *et al* and Houba *et al* taught enzymes and Tsuji *et al* specifically taught that esterases were involved in the conversion of CPT-11 or irinotecan into an active SN-38 drug that was known to be an anti-cancer agent. Houba *et al* specifically teaches that glucuronidases can be used in ADEPT. One of skill in the art would have found it obvious to combine the references because ADEPT was a well known and practiced method wherein the modification or variation within the method included the targeting moieties or antibodies, the enzymes, and the prodrug. Because it was known that CPT-11 was a well known anti-cancer agent that could be converted into an active agent (SN-38) with esterases, and because the method disclosed by Bagshawe required an inactive drug that could be converted by an enzyme a the target site, the combination of two well known methods and

products is obvious to combine. Further, it is know that in order for SN-38 to be cleared from the system, it needs to be hydrolyzed into glucuronide (as evidenced by Rivory *et al* Cancer Chemother Pharmacol 1995;36(2):176-179, see abstract) by glucuronidase. Therefore, absent undue experimentation, the combination of known products to perform a method that was well known in the art is considered obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
June 16, 2003

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